REMARKS

The Official Action dated August 20, 2003 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claim 42 has been amended to clarify the preamble and step (i) in accordance with the teachings through the present specification. Claims 44-46 and 60 have also been amended to more clearly define the invention limitations set forth therein. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 42-62 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserted that claim 42 was unclear as to whether a method claim or a use of a method claim was recited. The Examiner also asserted that in claims 44-46, the mixture was unclear and that claims 57 and 58 contradicted claim 42 in reciting predeposition of Reactant*. Finally, the Examiner asserted that claim 60 was vague and indefinite in recitation of "is capable of".

This rejection is traversed and reconsideration is respectfully requested. Claim 42 clearly recites a method for detecting an analyte in a sample in a flow matrix by use of biospecific affinity reaction. Moreover, the method comprises allowing an analytically detectable reactant (Reactant*) and a sample comprising the analyte to migrate through flow channels in a flow matrix to a detection zone. Claim 42 does not require the Reactant* to be included in the sample, whereby claims 57 and 58, which recite predeposition of Reactant*, do not contradict claim 42, but rather recite specific embodiments thereof. Claims 44-46 each recite an embodiment wherein a mixture of biospecific affinity reactants is immobilized

to the hydrophilic groups on the Capturer particles. As set forth in the specification, for example pages 6-7, such mixtures of biospecific affinity reactants are suitable for allergy tests wherein an analyte of IgE antibodies may be a complex mixture of up to 100 or more different proteins and a mixture of biospecific affinity reactants may suitably comprise a mixture of IgE allergens. Applicants submit that one of ordinary skill in the art will therefore find the reference to a mixture of biospecific affinity reactants in claims 44-46 as clear and definite. Finally, claim 60 recites that Reactant' is the firmly anchored Capturer or a reactant to which the Capturer binds by biospecific affinity. As biospecific affinity binding is well known in the art, Applicants submit that claim 60 is definite and clear to one of ordinary skill in the art.

It is therefore submitted that claims 42-62 are definite to one of ordinary skill in the art and particularly point out and distinctly claim the subject matter which Applicants regard as the invention, whereby the rejection under 35 U.S.C. §112, second paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 42-47, 51-53, 56, 57, 59-61, 63-68, 72-74, 77, 78 and 80-82 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Charlton et al U.S. Patent No. 5,989,921 in view of the Batz et al U.S. Patent No. 4,415,700 and the Brown et al U.S. Patent No. 5,149,622. The Examiner asserted that Charlton et al disclose an immunoassay method and device with a test site comprising latex particles entrapped or fixed in the flow path and having an immobilized protein (antibody/capturer) on their surface. The Examiner admitted that Charlton et al fail to teach immobilized particles which exhibit hydrophilic groups on their surfaces or that the particles have a size which is smaller than the smallest inner dimension of the flow channels of the matrix. The Examiner asserted that Batz et al disclose hydrophilic particles as a carrier for biologically and/or immunologically active substances

covalently bound to the particles for use in immunoassays. The Examiner asserted that Brown et al disclose a fluid device in which particles having a substance capable of reaction with an analyte in a sample are immobilized in a matrix, wherein a particle of a size smaller than the flow channels of the matrix is used to provide an improved solid-phase analytical device.

Claims 48, 50, 54, 55 and 69 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Devlin et al U.S. Patent No. 5,846,703. The Examiner asserted it would have been obvious to incorporate the use of immobilized antigens as taught by Devlin et al into the modified method of Charlton et al. Claims 49, 58, 70 and 79 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Dafforn et al U.S. Patent No. 4,981,786. The Examiner asserted it would have been obvious to incorporate the application of reagents and the detection of autoimmune antibodies as taught by Dafforn et al into the modified method of Charlton et al. Finally, claims 62 and 83 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Self U.S. Patent No. 4,446,231. The Examiner asserted it would have been obvious to use immunoassays as taught by Self for the diagnosis of autoimmune diseases.

However, Applicants submit that the methods and test kits defined by claims 42-83 are nonobvious over and patentably distinguishable from the combination of Charlton et al, Batz et al and Brown et al, even in further view of Devlin et al, Dafforn et al or Self. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 42, the present invention is directed to a method for detecting an analyte in a sample in a flow matrix by use of biospecific affinity reaction. The method comprises allowing an analytically detectable reactant (Reactant*) and

the sample comprising the analyte to migrate through channels in a flow matrix to a detection zone located in the matrix, in which there is a firmly anchored biospecific affinity reactant (Capturer), and capturing the Reactant* in the detection zone in an amount related to the amount of analyte in the sample. According to claim 63, the invention is directed to a test kit used for performing analytical methods in a flow matrix utilizing biospecific affinity reactions to detect an analyte in a sample. The kit comprises (i) a flow matrix having a detection zone in which there is firmly anchored biospecific affinity reactant (Capturer), and (ii) an analytically detectable reactant (Reactant*).

In both the claimed methods and test kits, the Reactant* has labeled particles as an analytically detectable group, and the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface. The particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone. Thus, the Capturer is predisposed in the flow channels of the flow matrix by the immobilized particles exhibiting hydrophilic groups on their surface. As set forth in the present specification, including the examples, such methods and test kits wherein the Reactant* has labeled particles as an analytically detectable group and the Capturer is anchored within the flow channels of the matrix by immobilized particles which exhibit hydrophilic groups on their surface, provide surprisingly improved analytical detection of an analyte in a sample.

Charlton et al disclose a test cell and a method for detection of a preselected ligand in a liquid sample. Charlton et al disclose that the method involves the step of transporting the sample and a conjugate comprising a protein bound to a metal sol or other colored particle along a flow path and in contact with a test site comprising immobilized binding protein specific to an epitope of the ligand. Charlton et al broadly disclose that the test site comprises

latex particles trapped or otherwise fixed in the flow path having the immobilized protein on their surface (column 3, lines 25-37), and specifically disclose the use of latex beads comprising polystyrene particles passively coated with purified rapid anti-human chorionic gonadotropin (column 7, lines 61-64).

However, Applicants find no teaching or suggestion by Charlton et al relating to a method or test kit as defined in claims 42 and 63 wherein a biospecific affinity reactant (Capturer) is firmly anchored to a flow matrix via immobilized particles exhibiting hydrophilic groups on their surface, particularly in combination with an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group. As discussed in the present specification, for example beginning at page 4, line 21, a hydrophobic particle such as the polystyrene employed by Charlton et al is absorbed very strongly to flow matrices such as nitrocellulose membranes. However, the hydrophobic features of the particles promote non-specific absorption of an analytically detectable reactant (Reactant*) and/or analyte and therefore decrease the sensitivity of test methodologies. In the present invention, the immobilized particles which anchor the Capturer to the matrix exhibit hydrophilic groups on their surface. As discussed beginning at page 5, line 8, introduction of the hydrophilic groups on the particles facilitates covalent binding of biospecific affinity reactants to the particles and decreases the tendency of non-specific absorption in the detection zone. Applicants find no teaching or suggestion by Charlton et al relating to immobilized particles exhibiting hydrophilic groups on their surface, or any advantage provided thereby.

The deficiencies of Charlton et al are not resolved by Batz et al and Brown et al. For example, Batz et al disclose hydrophilic latex particles consisting of a homo- or a co-polymer of monomers which are sparingly soluble in water and a process for the preparation of such

particles. Batz et al further disclose the use of such particles as carrier materials for biological and/or immunologically active substances in diagnostic agents. Particularly, as demonstrated in Examples 10-13 at columns 8-12 of Batz et al, the particles are used for solution immunoassays (see, for example, column 9, lines 50-60; column 10, line 58 - column 11, line 6; and column 11, lines 17-49). Applicants find no teaching or suggestion by Batz et al relating to a flow matrix immunoassay or use of the latex particles described therein in a flow matrix immunoassay. In fact, Applicants find no teaching or suggestion by Batz et al that their latex particles are suitable for adsorbtion to a second solid support or matrix. Moreover, Applicants find no teaching, suggestion or recognition by Batz et al that their particles will provide improved sensitivity in flow matrices and decrease the tendency of non-specific absorption in a detection zone as is obtained according to the present invention.

Brown et al disclose a solid-phase analytical device for use in solid-phase binding assays to determine the presence or amount of an analyte in a test sample. In the paragraph bridging columns 8 and 9, Brown et al disclose the use of substantially spherical solid particles retained and immobilized upon fibers of a porous fiber matrix material. Brown et al specifically disclose that

> "the size of the particles is not critical, and so long as the average diameter of the particles is substantially within the aforestated range (although it is preferred that the average diameter of the particles be smaller than the average pore size of the fibrous matrix), any type of particles having the foregoing properties is suitable for use" (column 9, lines 11-17).

The referenced range is from about 0.1 to about 10 microns or more, most preferably from about 0.1 to about 5 microns (column 8, lines 53-56). However, Applicants find no teaching by Brown et al that the particle size is smaller than the flow channels of the matrix or, as required by the present claims, that the particles have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix. To the contrary, Brown et al merely refer

to average diameters. Thus, Brown et al do not teach or suggest the limitations required by the present claims.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). As noted, Batz et al fail to teach or suggest the use of their latex particles in a flow matrix or in combination with any other type of solid support, and Brown et al fail to teach a method and flow matrix as presently claimed, wherein particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone. In view of these deficiencies, Batz et al and Brown et al in combination with Charlton et al do not enable one of ordinary skill in the art to make and use the presently claimed methods and test kits. It is therefore submitted that the methods and test kits defined by claims 42-47, 51-53, 56, 57, 59-61, 63-68, 72-74, 77, 78 and 80-82 are nonobvious over and patentably distinguishably from the combination of Charlton et al, Batz et al and Brown et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Moreover, the deficiencies of Charlton et al in view of Batz et aland Brown et al are not resolved by any of the additional references cited by the Examiner. For example, Devlin et al disclose fluorescence immunoassays using fluorescent dyes free of aggregation and serum binding. Devlin et al broadly disclose that the sandwich techniques disclosed therein can be used to assay antibodies rather than antigens wherein the antigen coupled to a solid phase is used as a first receptor. Beginning at column 4, line 56, Devlin et al briefly discuss the use of enzyme-enhanced fluorescence technology which combines microparticle capture

and antigen-antibody reaction with an enzyme rate reaction using a fluorescent enzyme substrate.

However, Applicants find no teaching or suggestion by Devlin et al relating to a method or test kit as presently claimed, or for modifying the teachings of Charlton et al to provide such a method or test kit. Particularly, Applicants find no teaching or suggestion by Devlin et al for a method or test kit employing a flow matrix as presently claimed wherein an analytically detectable reactant (Reactant*) has labeled particles as an analytically detectable group and a biospecific affinity reactant (Capturer) is anchored to the flow matrix via immobilized particles of a size and function as claimed and exhibiting hydrophilic groups on their surface. Similarly, Applicants find no teaching or suggestion by Devlin for modifying the teachings of Charlton et al to provide such a combination, or relating to any benefit provided by either a flow matrix method or test kit employing such a combination.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*. The cited combination of Charlton et al, Batz et al, Brown et al and Devlin et al does not enable one skilled in the art to conduct the claimed methods or to make and use the claimed test kits. Thus, these references do not in combination render the presently claimed methods and test kits obvious. It is therefore submitted that the rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Devlin et al has been overcome. Reconsideration is respectfully requested.

Dafforn et al disclose a multiple port assay device for capturing a first member of a specific binding pair in a zone and for allowing liquid to be transported by capillary action away from the zone. Delivery of a sample may be made into the device through a first means using a dropper, syringe needle, etc., resulting in deposit of the sample on a bibulous strip,

and a liquid reagent other than sample may be added to the device through a second means. Additional liquid reagents may be added to the device either before or after sample addition, at least one of such reagents being added through the means not used for adding the sample (column 13, lines 32-42).

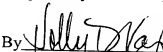
However, Applicants find no teaching or suggestion by Dafforn et al relating to a method or test kit as presently claimed employing, in combination, an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group and a Capturer which is anchored to the matrix by immobilized particles as defined and exhibiting hydrophilic groups on their surface. Similarly, Applicants find no teaching or suggestion by Dafforn et al relating to any improvement provided by a method or a test kit employing such a Reactant* and immobilized Capturer in combination. Finally, Applicants find no teaching or suggestion for modifying the teachings of Charlton et al to incorporate any or all of the teachings of Dafforn et al, and particularly Applicants find no teaching or suggestion in either reference for modifying the teachings of Charlton et al along the lines of the presently claimed methods and test kits. In view of these deficiencies in the teachings of Dafforn et al, the combination of Dafforn et al with Charlton et al, Batz et al and Brown et al does not enable one of ordinary skill in the art to perform the presently claimed methods or to make and use the claimed test kits. Thus, the combination of Charlton et al, Batz et al, Brown et al and Dafforn et al does not render the presently claimed methods and test kits obvious under 35 U.S.C. §103. It is therefore submitted that the rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Dafforn et al has been overcome. Reconsideration is respectfully requested.

Finally, Self discloses an immunoassay using an amplified cyclic detection system. At column 1, beginning at line 39, Self broadly discloses that immunoassays may be used for

qualitative or quantitative determinations and that color reactions and precipitation reactions, for example, using latex particles for visualization, may be used. However, Applicants find no teaching or suggestion by Self relating to methods or test kits as presently claimed employing a combination of an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group and a biospecific affinity reactant (Capturer) anchored to a flow matrix via immobilized particles as claimed which exhibit hydrophilic groups on their surface. Similarly, Applicants find no teaching or suggestion by self for modifying the teachings of Charlton to provide such methods or test kits, or relating to any advantage provided thereby. Thus, the combination of Charlton et al, Batz et al, Brown et al and Self does not enable one of ordinary skill in the art to conduct the presently claimed methods or to make and use the presently claimed test kits. Accordingly, the combination of Charlton et al, Batz et al, Brown et al and Self does not render the presently claimed methods and test kits obvious. It is therefore submitted that the rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Self has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§ 103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

By 

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